CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-302

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-302 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 11/01/01

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/15/00	12/19/00	12/20/00
AMENDMENT/BC	03/08/01	03/09/01	03/15/01
AMENDMENT/BC	05/21/01	05/21/01	05/22/01
AMENDMENT/BC	05/29/01	05/30/01	05/30/01
AMENDMENT/BL	06/19/01	06/21/01	06/21/01
AMENDMENT/BI	07/06/01	07/09/01	07/09/01
AMENDMENT/BC	07/12/01	07/13/01	07/17/01
AMENDMENT/BC	08/07/01	08/08/01	08/08/01

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

DRUG PRODUCT NAME

Proprietary:	Elidel
Nonproprietary/USAN:	pimecrolimus
Code Names/#'s:	ASM-981
Chem.Type/Ther.Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: Atopic Dermatitis

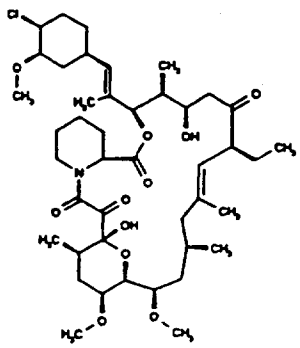
DOSAGE FORM: Cream

STRENGTHS: 1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: x Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

APPEARS THIS WAY
ON ORIGINAL

NDA 21-302
Novartis Pharmaceuticals Corp.
Elidel Cream 1%



Molecular formula: $C_{43}H_{68}ClNO_{11}$
Mol. Wt.: 810.47
Systematic Chemical Names:

IUPAC

(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-[(1R,3R,4S)-4-chloro-3-methoxycyclohexyl]-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

CAS

(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- 3-[(1E)-2-[(1R,3R,4S)-4-chloro-3-methoxycyclohexyl]-1-methylethenyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone (9CI)

2.1.2. Other names

[3S-3R*[E(1S*,3S*,4R*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]- 3-[2-(4-chloro-3-methoxycyclohexyl)-1-methylethenyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone

33-epi-chloro-33-desoxyascomycin

Table 3

DMF INFORMATION

DMF #	DMF Holder	TYPE	LOA Date	Date Of Last Review
—	[ ]	II	16-Nov-00	See microbiology review, 5/30/01
—	[ ]	III	14-Nov-00	2/14/01

NDA 21-302
Novartis Pharmaceuticals Corp.
Elidel Cream 1%

DMF #	DMF Holder	TYPE	LOA Date	Date Of Last Review
	[ ]			
—	[ ]	III	28-Nov-00	None
—	[ ] Polypropylene cap	III	17-Nov-00	2/20/01
—	[ ]	III	17-Nov-00	2/23/01

RELATED DOCUMENTS (if applicable):

IND — (ASM 981 Cream 1% for Atopic Dermatitis), Novartis Pharmaceutical Corporation
IND —
IND —
IND —

CONSULTS:

(1) The project manager requested a microbiology consult on 1/30/01 to review microbial limit test (see Vol. 1.4; pg. 4-193). This issue was addressed in the 5/30/01 microbiology review.

(2) Chemist requested additional microbiology consult on 2/26/01 to review the ——— of the starting material, ——— [see DMF — and ——— manufacturing process in the subject NDA (Vol. 1.3; pg. 4-122)] Microbiology review was completed on 5/30/01.

REMARKS/COMMENTS:

The applicant submitted a New Drug Application for Elidel Cream 1% for the treatment of Atopic Dermatitis. This NDA has 1S classification. A comprehensive description of the CMC information was submitted for this drug product in support of this NDA.

NDA 21-302
Novartis Pharmaceuticals Corp.
Elidel Cream 1%

Even though the CMC information was comprehensive, deficiencies were observed for both drug substance and drug product. These deficiencies were in the areas of manufacturing, packaging, specifications, and stability (see chemist review notes below). Having said this, the drug substance deficiencies have been corrected; see amendment dated 5/21/01 below. The drug product deficiencies remained open.

Furthermore, the applicant submitted additional amendments to update the NDA. These amendments were reviewed and are summarized as follows:

- Amendment/BC dated 3/8/01- Provided additional information requested by the FDA on 1/23/01 regarding the [redacted] forms of pimecrolimus drug substance; see review notes below

- Amendment/BC dated 5/21/01- provided additional information requested by FDA's IR letter dated 5/3/01 regarding CMC deficiencies found in the drug substance; see review notes below

- Amendment/BC dated 5/29/01- provided replacement documentation for inclusion to more accurately represent the manufacturing process that is presently being used to manufacture pimecrolimus drug substance; see review notes below

- Amendment/BL dated 06/19/01- provided revised draft labeling for the package insert and the latest color representation of carton and container labeling; see review notes

- Amendment/BI dated 07/06/01- provided information as requested by the microbiologist (see Microbiologist Review dated 5/30/01).

- Amendment/BC dated 07/12/01- provided additional stability data to support the proposed 24-month expiration date.

- Amendment/BC dated 08/07/01- provided batch analysis documentation as the result of a GMP inspection that took place on July 2-4, 2001, whereby the inspector requested this information.

Methods Validation is pending; to be initiated as soon as possible.

EER was found acceptable on 9/14/01 for the facilities as listed below.

NDA 21-302
Novartis Pharmaceuticals Corp.
Elidel Cream 1%

CONCLUSIONS & RECOMMENDATIONS:

The NDA is found approvable from a manufacturing and controls standpoint. However, minor deficiencies in the CMCs have been observed in the drug product. These CMC deficiencies were communicated to the applicant by fax on 10/24/01.

Ernest G. Pappas

Review Chemist

cc: Orig. NDA 21-302
HFD-540/Division File
HFD-540/Pappas
HFD-540/MO/Cook
HFD-540/Pharm/Hill
HFD-540/Micro
HFD-540/PM/Wright
R/D Init by: Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ernest G. Pappas
11/1/01 11:59:48 AM
CHEMIST
I have completed my chemistry review and I am recommending approval.

Wilson H. DeCamp
11/1/01 12:05:36 PM
CHEMIST
concur with review

APPEARS THIS WAY ON ORIGINAL

NDA 21-302

Elidel (pimecrolimus) Cream 1%

Novartis Pharmaceutical Corporation

Ernest G. Pappas
Division of Dermatological and Dental Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-302

2. Review #: 2

3. REVIEW DATE: 11/28/01

4. REVIEWER:
   Ernest G. Pappas

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	15-Dec-2000
Amendment (BC)	08-Mar-2001
Amendment (BC)	21-May-2001
Amendment (BC)	29-May-2001
Amendment (BL)	19-Jun-2001
Amendment (BI)	06-Jul-2001
Amendment (BC)	12-Jul-2001
Amendment (BC)	07-Aug-2001
Telecon/Fax (IR)	24-Oct-2001

6. SUBMISSION (S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BC)	01-Nov-2001

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceutical Corporation
Address:	59 Route 10 East Hanover, New Jersey 07936-1080
Representative:	Ms Sheryl LeRoy

Telephone: (973) 781-2735

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Elidel
b) Non-Proprietary Name (USAN): pimecrolimus
c) Code Name/# (ONDC only): ASM-981
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Atopic Dermatitis

11. DOSAGE FORM: CREAM

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: x Rx ___OTC

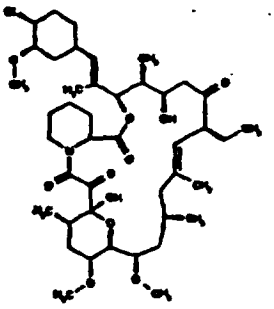
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

_____**SPOTS product – Form Completed**

__x Not **a SPOTS product**

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

APPEARS THIS WAY
ON ORIGINAL



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33-epi-chloro-33-deoxyascomycin

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	[ ]	Polypropylene caps	3	Adequate	20-Feb-2001	
—	III	[ ]		3	Adequate	23-Feb-2001	
—	III	[ ]		1	Inadequate	None	IR letter being drafted - CMC deficiencies
—	III	[ ]		3	Adequate	14-Feb-2001	
—	II	[ ]		1	Adequate	30-May-2001	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: (related)

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	—	ASM 981 Cream 1% for Atopic Dermatitis
IND	—	[ ]
IND	—	
IND	—	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	31-Oct-2001	Langille
EES	Acceptable	27-Aug-2001	Ambrogio
Methods Validation	Sent to [redacted] Laboratory; results pending	07-Nov-2001	Pappas

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-307

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be **approved** from a Chemistry standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product:

The drug product, Elidel (pimecrolimus) Cream 1%, is packaged in ——— ——— tubes with a white, propylene, piercing screw cap. This drug product was submitted as an NME since the active pharmaceutical was first of its class in this country for the treatment of atopic dermatitis. This NDA has a 1S classification.

The applicant proposed a 24-month expiration date for the product to be marketed in — 15 g, 30 g, and 100 g tubes. Acceptable stability data were submitted to support the proposed expiration date. In this regard, a 24-month expiry date has been granted for the finished product.

The tradename, Elidel, has been found acceptable by OPDRA. This labeling information, as well as the labels of the container and carton, is acceptable from a technical standpoint. The storage condition of 25^0 C (77^0 F), with excursions permitted between 15^0 C-30^0 C (59^0 F-86^0 F) and "Do not freeze" statement has found to be appropriate for the Elidel Cream 1%.

The labeling was reviewed and found acceptable by DDMAC.

Establishment Inspection: All facilities, as indicated in the NDA, were found acceptable for CGMPs. An overall recommendation of approvable was received from the Office of Compliance on 28-Aug-2001.

Environmental Assessment: The applicant's claim of categorical exclusion under regulation 21 CFR 25.31 (b) is acceptable since the EIC projection was found to be at a level well below 1 ppb.

(2) Drug Substance:

The drug substance, pimecrolimus, is an NME. The manufacture of pimecrolimus API consists of [redacted] In this regard, starting material [redacted] results from [redacted] This [redacted] process has been found to be acceptable (see Micro Review dated 31-Oct-2001). The synthesis and purification of the — pimecrolimus was adequately described in the NDA (see chemistry review #1, pg. 29).

[redacted]

The structure and physicochemical characteristic are adequately described in the NDA to assure the identity, strength, quality and purity of the pimecrolimus API.

[redacted]

Pimecrolimus is essentially insoluble in water. It is highly soluble in various alcohols, [redacted] It is somewhat less soluble in less hydrophilic solvents. [redacted]

[redacted]

B. Description of How the Drug Product is Intended to be Used

The drug product is to be administered topically as anti-infective agent for the treatment of atopic dermatitis.

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing and controls as identified above are sufficient to assure the consistent identity, strength, quality and purity of the drug.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

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III. INVESTIGATIONAL FORMULATIONS

Acceptable per Chemistry review #1, 01-Nov-2001

IV. ENVIRONMENTAL ASSESSMENT

Acceptable per Chemistry review #1, 01-Nov-2001

V. METHODS VALIDATION

Methods validation packages were sent the —— Laboratories on 11-Nov-2001.
Waiting validation report.

VI. LABELING

Acceptable per Chemistry review #1, 01-Nov-2001

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ON ORIGINAL

VII. ESTABLISHMENT INSPECTION

Application: NDA 21302/000 Priority: 1S Org Code: 540
Stamp: 15-DEC-2000 Regulatory Due: 15-OCT-2001 Action Goal: District Goal: 16-AUG-2001
Applicant: NOVARTIS PHARMACEUTICALS CO Brand Name: ELIDEL (PIMECROLIMUS) CREAM 1%

NO CITY, XX
Established Name:
Generic Name: PIMECROLIMUS
Dosage Form: CRM (CREAM)
Strength: 1%

FDA Contacts: M. WRIGHT (HFD-540) 301-827-2020, Project Manager
E. PAPPAS (HFD-540) 301-827-2066, Review Chemist
W. DECAMP II (HFD-540) 301-827-2041, Team Leader

Overall Recommendation:
ACCEPTABLE on 27-AUG-2001by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted] DMF No: ———
AADA No:

Profile: CFN OAI Status: NONE Responsibilities: ———
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JAN-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Establishment: 9617734 DMF No:
NOVARTIS PHARMA GmbH AADA No:
OEFLINGER STRASSE 44
WEHR, BADEN, GM D-79664

Profile: OIN OAI Status: NONE Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: OC RECOMMENDATION FINISHED DOSAGE PACKAGER
Milestone Date: 24-AUG-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Establishment: 9692043 DMF No:
NOVARTIS PHARMA INC (CIBA) AADA No:
SCHAFFHAUSERSTRASSE
CH-4332 STEIN, SZ

Profile: CRU OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION FINISHED DOSAGE RELEASE TESTER
Milestone Date: 02-AUG-2001

APPEARS THIS WAY
ON ORIGINAL

Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-AUG-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Establishment: 9611204 DMF No:
NOVARTIS PHARMA INC (SANDOZ) AADA No:
LICHSTRASSE 35, ST. JOHANN SITE
BASEL, SZ 4002

Profile: CRU OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION MANUFACTURER
FINISHED DOSAGE RELEASE
Milestone Date: 02-AUG-2001
TESTER
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-AUG-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Establishment: 9612715 DMF No:
NOVARTIS PHARMA INC (SANDOZ) AADA No:

RINGASKIDDY/CORK, RINGASKIDD

Profile: CTL OAI Status: NONE Responsibilities: DRUG SUBSTANCE RELEASE
Last Milestone: OC RECOMMENDATION TESTER
Milestone Date: 25-JAN-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Establishment: 9614433 DMF No:
NOVARTIS PHARMANALYTICA SA AADA No:

LOCARNO, SZ

Profile: CTL OAI Status: NONE Responsibilities: DRUG SUBSTANCE STABILITY
Last Milestone: OC RECOMMENDATION TESTER

Milestone Date: 11-JAN-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Establishment: DMF No:
[ ] AADA No:

Profile: OIN OAI Status: NONE Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-FEB-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Establishment: DMF No:
[ ] AADA No:

Profile: CTL OAI Status: NONE Responsibilities: [redacted]

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **18-APR-2001**

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

[redacted]

VIII. DRAFT DEFICIENCY LETTER

Not applicable

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ernest G. Pappas
12/6/01 08:30:04 AM
CHEMIST
recommend approval

Wilson H. DeCamp
12/6/01 08:32:28 AM
CHEMIST
concur with review

APPEARS THIS WAY
ON ORIGINAL